Mònica Grau González

METRONOMIC CHEMOTERAPY

INTRODUCTION & AIMS:

Metronomic chemotherapy (MC) is an **anti-tumor therapy**. It is a conventional chemotherapy modification that uses **lower** anticancer drugs **doses** and **minor breaks** between them, so drugs are administrated daily or every few days. These changes allow to **reduce toxicity**, to avoid drug resistance and **oral administration** too.

The project objectives are showing a new and booming chemotherapy, their characteristics and to establish protocols for use thereof.

ANTITUMOR EFFECTS

Inhibition of vasculogenesis and angiogenesis	• ↑ Tromboespondine 1 (TSP-1) • ↓ Ciclooxigenase 2 (COX – 2) • ↓Tirosin Kinase (TK)
Activation of immunity	• ↓ regulator T- Cells • ↑ Dendritic cells • ↑ Citotoxic T – Cells

ADVERSE EFFECTS

Grade 1	Vomiting, Anorexia, Diarrhoea, Lethargy
Grade 2	Vomiting, Anorexia, Diarrhoea, ↑ creatinine,
Grade 3	Neutropenia, Thrombocytopenia, Sterile hemorrhagic cystitis
Grade 4	Hemorrhagic colitis, sterile hemorrhagic cystitis (SHC)

Grade 5 (the most severe) → **not shown**

DRUGS,TUMOURS & OUTCOME IN DOGS

Drug & Dosage + Adjuvant	Tumour	Outcome
Ciclophosphamide (CYC) 12.5 – 25 mg/m²/24h 3w + Etoposide + Piroxicam	Hemangiosarcoma	Median Survival Time (MST): 178 d. 15% SHC
CYC10 mg/m²/24 – 48h + Piroxicam	Soft tissue sarcoma	Minimum Disease- Free interval (MDFI): 410 d. [Without MC, only surgery MDFI: 211 d]. 12% SHC
CYC 12.5 - 15 mg/m²/24h + None	Soft tissue sarcoma	Not assessed
Chlorambucil 4mg/m²/24h + COX inhibitors or none	transitional cell carcinoma of bladder	Stable disease (SD): 67%, Partial response (RP): 3% MST: 221d.

MOST COMMONLY USED DRUGS AND THEIR EFFECTS

Drug	Antitumor Effects
Ciclophosphamide	↑TSP-1, ↓recruitment CPEs, ↑Immune system
Non Steroidal Anti Inflammatory Drugs	↓COX
TK Inhibitors	Block TK receptors

CONCLUSIONS

Metronomic chemotherapy is not an attack therapy, it's a maintenance treatment

Experimental alternative to conventional chemotherapy against solid tumours, leukemia and metastatic tumours, with less toxicity.

New attack targets are being looked for

REFERENCES

•Bertolini F., Paul S., Mancuso P., Monestiroli, S., Gobbi, A., Shaked, Y., y Kerbel, R.S. 2003. Maximum tolerable dose and low-dose metronomic chemotherapy have opposite effects on the mobilization and viability of circulating endothelial progenitor cells. *Cancer Res, 63: 4342-4346.*

•Browder, T., Butterfield, C. E., Kraling, B. M., Shi, B., Marshall, B., O'Reilly, M. S., and Folkman, J. 2000. Antiangiogenic scheduling of chemotherapy improves efficacy against experimental drug-resistant cancer. *Cancer Res, 60: 1878–1886.*

•Fidler IJ, Ellis LM. 2000. Chemotherapeutic drugs: more really is not better. *Nat Med, 6: 500–02.*

•Hanahan D, Bergers G, Bergsland E. 2000. Less is more, regularly: metronomic dosing of cytotoxic drugs can target tumor angiogenesis in mice. *J Clin Invest., 105: 1045–47.*